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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/479,995	06/07/95	PERGOLIZZI R	ENZ-(D1)(C2)

HM31/1027

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EXAMINER
MARSCHEL, A

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/27/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/479,995	Applicant(s) Pergolizzi et al.
	Examiner Ardin H. Marschel	Group Art Unit 1634

[X] Responsive to communication(s) filed on *Jun 24, 1998*.

[ ] This action is **FINAL**.

[ ] Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

[X] Claim(s) *283-362, 364-380, 382-398, 400-404, 406-439, and 441-505* is/are pending in the application.

[redacted], Claim(s) *1-282, 363, 381, 399, 405, and 440 have been* canceled.

[X] Claim(s) *364-380, 382-398, 400-404, 406-410, 439, 442-460, and 479-487* is/are allowed.

[X] Claim(s) *283-296, 298-301, 304, 306, 307, 309-321, 323-333, 335-340, 343-347, 350, 353, 358-362, 411-419, 422, 423, 426, 427, 434-438, 441, 461-475, and 488-505* is/are rejected.

[X] Claim(s) *297, 302, 303, 305, 308, 322, 334, 341, 342, 348, 349, 351, 352, 354-357, 420, 421, 424, 425, 428-433, and 476-478* is/are objected to.

[ ] Claims _____ are subject to restriction or election requirement.

Application Papers

[ ] See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

[ ] The drawing(s) filed on _____ is/are objected to by the Examiner.

[ ] The proposed drawing correction, filed on _____ is [ ]approved [ ]disapproved.

[ ] The specification is objected to by the Examiner.

[ ] The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

[ ] Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

[ ] All [ ] Some* [ ] None of the CERTIFIED copies of the priority documents have been

[ ] received.

[ ] received in Application No. (Series Code/Serial Number) _____.

[ ] received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

[ ] Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

[ ] Notice of References Cited, PTO-892

[ ] Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

[ ] Interview Summary, PTO-413

[ ] Notice of Draftsperson's Patent Drawing Review, PTO-948

[ ] Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.129(a). Applicants' submission after final, filed on 6/29/98, has been entered.

Applicants' arguments, filed 6/29/98, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either newly applied or reiterated. They constitute the complete set presently being applied to the instant application.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 283-296, 298-301, 304, 306, 307, 309-321, 323-333, 335-340, 343-347, 350, 353, 358-362, 411-419, 422, 423, 426, 427, 434-438, 441, 461-475, and 488-505 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Dunn et al.

This rejection is maintained and reiterated from the previous office action, mailed 6/22/98, regarding the instant composition and kit claims and added against the newly added

claims for reasons given as follows. It is noted that applicants have amended claims such as 283 to require that the second part of the claimed composition of matter contains "one or more non-radioactive signal generating portions". It is noted that the second part is not limited to being fully non-radioactive but rather only "portions" thereof. It is also noted that radioactive labeling as practiced in Dunn et al. also does not result in every nucleotide being P^{32} labeled in the signalling segments therein disclosed. Such non-radioactive portions also are capable of hybridizing to nucleic acid segments themselves with signalling entities thereon. It is again noted from previous office actions that compositions or kits are rejected in the above cited instant claims and that inherent capabilities, that are also present in a reference such as Dunn et al., or the novel "naming" of various segments do not confer patentable weight. Thus, the Dunn et al. second part also contains "non-radioactive portions" and therefore are "second parts" such as cited within instant claims 283 etc. Now applicants' arguments will be responded to. Applicants argue that the newly added claims are based on claims only previously objected to as depending from rejected claims in order to submit them in independent form. One such previously objected to claim is 297 on which these new claims are based. It is noted that claim 297 is limited to bacterium or bacterial component practice but claim 464, for example, is not limited as such but rather includes viral components in line 6 which is deemed to include viral

polynucleotide segments. Claim 302 is also cited as being the basis for newly added claims. Claim 302 is directed to antigen or antibody practice but newly added claim 464, for example, includes much more than antigen or antibody practice such as a polynucleotide sequences in the last three lines therein. Thus, many of the newly added claims are included herein due to the breadth of claims that have been newly submitted and not limited to limitations only from previously objected to claims. The newly added kit claims 488-505 still only contain components as previously rejected in composition or kit claims and are therefore rejected hereinunder. Applicants also argue that P^{32} labeling is not artificial alteration. This is non-persuasive because such a label is clearly artificial and clearly an alteration from an unlabeled oligo- or polynucleotide.

Claims 297, 302, 303, 305, 308, 322, 334, 341, 342, 348, 349, 351, 352, 354-357, 420, 421, 424, 425, 428-433, and 476-478 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 364-380, 382-398, 400-404, 406-410, 439, 442-460, and 479-487 are allowed.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

October 23, 1998

Ardin H. Marschel

ARDIN H. MARSCHEL
PRIMARY EXAMINER

The art unit designated for this application has changed. Applicant(s) are hereby informed that future correspondence should be directed to Art Unit 1809.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification, as originally filed, does not provide support for the invention as is now claimed.

In claim 300, lines 3-4, the phrase "an analog-containing polymer" which adds NEW MATTER in that written basis for generic polymers containing analogs has not been found. Consideration of the support cited by applicants reveals that polynucleotides of various types are listed but not more generic polymers. Another interpretation is that NEW MATTER is added via unclarity of the metes and bounds of such polymers. Claims 315, 321, and 328 also contain this NEW MATTER and claims 317 and 318 via dependence from the above claims.

In claim 313, line 2, the phrase "partially double-stranded" is given. Consideration of the written support as filed has failed to reveal any written basis for "partially" double-stranded. This "partially" is thereofore NEW MATTER. Claims 319 and 331 also contain this NEW MATTER.

Claims 365, 383, 401, and 407 are directed to a specific order of complex formation wherein the bridging entity is first contacted with the signalling entity to form a first complex followed by contacting this first complex with the analyte. Consideration of the support cited by applicants on pages 33-34 has not revealed a written basis for this order of complex formation. Therefore the limitations in claims 365, 383, 401, and 407 directed to the above summarized order lack written basis as filed and contain NEW MATTER and claims 404 and 410 via dependence from the above claims.

Claim 300, 313, 315, 317-319, 321, 328, 331, 365, 383, 401, 404, 407, and 410 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the above objections to the specification.

Claims 283-438 are rejected, as discussed below, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 287, line 2, "more than one molecular bridging entity" is cited. In lines 7-8, "said bridging entity" is cited. This citation in lines 7-8 lacks antecedent basis because it directs this portion of the second part of the claimed composition to "said bridging entity" as a single item. Confusingly, there is no such "single" bridging entity described previously in the claim. Instead line 2 cites multiple bridging entities via the phrase "more than one". It is unclear which

bridging entity is intended in lines 7-8 out of the multiple bridging entities cited in line 2. Lines 7-8 suggest that there is some particular bridging entity that is being referred to. Since there are only multiple bridging entities in line 2, the is no antecedent basis for the liness 7-8 citation of a particular or single bridging entity. Claims 288-290 also contain this unclarity as well as claims dependent therefrom. Clarification of this via clearer claim wording is requested.

Claims 283 etc. cites "a first part" and "a second part" wherein each "part" contains portions wherein the relationship(s) between these portions are undefined in the claims. See the below specific claim 291 explanation as an example of the unclarity in the definition of each "part" as given in the instant claims.

Claim 291, lines 8-9, cite "one or more polynucleotides..." but without defining their relationship to the portion that is capable of binding or hybridizing with the bridging entity. Since line 6 of claim 291 cites "a second part", this is suggestive of part (singular). Such a singular part would be expected to contains portions that are attached, linked, bound together, or related in some way. No such relationship has been defined between the two portions of the "part" of lines 6-9 of claim 291. Do applicants intend that lines 6-9 of claim 291 disclose a singular part or, alternatively, a part made up of portions which are not required to be attached or related in some way? A "part" made up of unrelated portions is vague and

indefinite because this is interpretable as "parts" but is confusingly not cited in the claim as "parts". Another unclarity is that line 6 cites the second part as comprising "more than one signalling entity", each such entity comprising...", but confusingly lacks any designation of what performs the signalling function thereafter in the claim. Claims 292-294 also contain the above unclarities as well as claims dependent therefrom. Clarification is requested via clearer claim wording.

Claims 300 and 310 are vague and definite beyond the above unclarities in that the respective lines 1 cite "said nucleic acid" without clear antecedent basis. It is noted that several nucleic acids are given in the claims from which claims 300 and 310 depend directly or indirectly such as in the analyte in claim 299 and in the molecular bridging and signalling entities. Clarification of the claim wording is requested as to the antecedent basis

Claim 322 etc. is vague and indefinite beyond the above unclarities in that it is unclear what the metes and bounds of the word "derived" are as cited in line 3 therein. Many other claims cite this word also. If there are no limitations on what may be deleted, replaced, or added; such derivation may result in any other composition whatsoever. If that is so, why cite what is being altered as derived? Clarification of what is intended for such derivation practice is requested.

Claim 356 lacks antecedent basis for a singular "molecular bridging entity" wherein claims 287 etc. cite multiple molecular

bridging entites.

Claims 360-362 contain the above unclarities but also are vague and indefinite as to what is meant in that claims 360-362 and claims 283, 284, 291, and 293 appear to be identical except for what the claimed subject matter is called in their respective first lines. For example, in claim 283 the subject matter is a "composition of matter" whereas in claim 360 the subject matter is an "article of manufacture". What difference is meant thereby? Does claim 360 indicate that a manufacturing process in required to prepare the claimed article whereas manufacturing is not required for preparing the composition of claim 283? If manufacturing is not required, is this suggestive that claim 283 includes products of nature within its scope? Clarification of the metes and bounds of each of these types of claims compared to each other is requested.

Claim 438 is vague and indefinite as to what the metes and bounds are for the phrase "nucleic acid analog". Is this meant to be directed to analogs that are no longer nucleic acids but have some nucleic acid type characteristic(s)? Is this meant to be directed to nucleic acids that are modified as compared to naturally occurring nucleic acids? Aren't modified nucleic acids still nucleic acids? What differentiates nucleic acids from nucleic acid analogs? Similarly, in claim 315, line 4, the phrase "an analog-containing polymer" is cited without defining what it is an analog of. A polymer is still a polymer even if modified, isn't it? What is an analog of a polymer? Similarly,

the term "modified" is given in claim 317, line 2, without defining what modifications are practicable therein. What are the metes and bounds of such modifications? Numerous instant claims contain the above unclarities and are rejected also hereinunder. Clarification is requested.

Claims 364, 365, 382, and 383 cite the phrase "said complex" in their respective last lines. This "said complex" lacks clear antecedent basis because two complexes are cited that may be the antecedent. One complex is the "first complex" in line 3 of claims 364, 365, 382, and 383 and a second complex is given in line 4 of claims 363 and 381 from which claims 364, 365, 382, or 383, respectively, depend. Claim 400 contains a similar unclarity.

Claims 283-438 cite the phrase "nucleic acid sequences or segments" either directly or indirectly via claim dependence. This phrase is vague and indefinite as what difference is intended between "sequences" and "segments". Since these are separately cited in the claims, this indicates that a different meaning is intended for each of these items. It is unclear what this different meaning may be. Clarification is requested.

Claims 367 and 368, lines 1-2 of each, contain the phrase "wherein said detecting step the direct" which is awkwardly worded such that it is unclear what is meant thereby. Claims 369, 371-373, 385-387, and 389-391 also contain similar confusing wording.

Claims 374 and 392 are vague and indefinite due to unclarity

of what is meant by the phrase "and a binding step on an insoluble phase". Is this intended to indicate that a binding step is present only within the detecting step of the process or is this intended to indicate that the binding may occur anywhere in the process? It is noted that claim 65, as filed, as pointed to by applicants indicates that the detecting step per se is only limited to comprise a binding step on an insoluble phase. Clarification is requested.

Claims 343-346 are vague and indefinite because it is unclear what is meant by citing the word "indirectly" twice in the last line of claim 343. Does this indicate that at least two linkages are required between the signalling entity and the actual signal producing entity? or some other indirect procedure? Clarification is requested.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 283-296, 298-301, 304, 307, 309-321, 323-333, 335-340, 347, 350, 353, 358-364, 366, 367, 372-376, 378-382, 384, 385, 392-394, 396-400, 402, 403, 405, 406, 408, 409, and 438 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Dunn et al.

Dunn et al. reads on the above listed claims due to its

disclosure of an immobilized target analyte wherein a bridging entity is hybridized thereto followed by washing and then the hybridization of a nick translated radiolabelled signalling entity that is made up of a heterogeneous mixture of radiolabelled fragments produced as a result of the nick translation process. This nick translation process also results in a ratio of signalling entities as being clearly greater than 1 as compared to bridging entities, but is unclear how much greater than 1.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 283-301, 304, 307, 309-340, 343-364, 366, 367, 370-376, 378-382, 384, 385, 388, 390-394, 396-400, 402, 403, 405, 406, 408, 409, 411, 413, 414, 416, 418-438 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Dunn et al.(1977) taken in view of Ward et al.(P/N 4,711,955).

The instant invention is directed to compositions for detecting an analyte via the recognition and binding of a bridging entity to the analyte. The bridging entity contains two portions, one portion that recognizes and binds the analyte and a second portion containing a polynucleotide segment. The polynucleotide segment of the second portion of the bridging entity hybridizes to a signalling entity via a complementary nucleic acid segment in the signalling entity. The signalling entity may be non-radioactively labeled so as to be detectable. The detection of the label indicates the presence of analyte. Kit-like compositions for the practice of the method are also claimed. The specific limitations of certain claims are discussed below as to how they are made obvious by the above combination of references. It is noted that instant claim 283 includes a bridging entity with only one second nucleic acid portion within its scope, but even claims such as instant claim 287 which cites multiple bridging entities lacks limiting these multiple entities as including different types or sequences, thus permitting a solution of identical molecules yet within the scope of claim 287. Also, it is noted that the second part of instant claim 283 gives the signalling part as comprising more than one

signalling entity but without requiring either that they must include non-identical entities or that they must contain entities that bind or hybridize to different segments of the second portion of the bridging entity.

Dunn et al.(1977) disclose a sandwich hybridization technique wherein an RNA construct containing two portions performs as a bridging entity as in the instant invention. The two portions of the RNA construct consist of an analyte recognition and binding portion and a tail as discussed on page 23, bridging paragraph between the first and second columns. The tail is a polynucleotide segment that hybridizes to a radiolabeled signalling entity for detection. The detection of the radiolabel is indicative of analyte detection. This methodology is depicted in Dunn et al.(1977) on page 24 in Figure 1 with detection results shown in Figures 2 etc. in the reference. This reference generically discloses the instant invention at said page 23 citation but lacks the use of a non-radioactively labeled signalling entity. Additionally, the generic scope of practice of the sandwich hybridization technique of Dunn et al.(1977) is suggested in that the page 23 summary of the technique is generic in nature and the system disclosed by Dunn et al.(1977) to illustrate the technique is stated as being a "model system" on page 23, second column, line 9. These disclosures clearly suggest a scope broader than that of detecting viral RNA map transcription sites as given in the experimental examples in the reference and include detection of

other target sites in genomes of organisms such as bacteria etc. It is noted that the radiolabelled signalling entities of Dunn et al.(1977) are prepared via nick translation as is an embodiment of biotin labelling in the below given Ward et al. disclosure.

Ward et al. generically discloses the substitution of biotinylated nucleic acids as a non-radioactive label for radiolabeled nucleic acids in hybridization detection methods. The disclosure of Ward et al. includes several motivations for the substitution of non-radioactive labels such as based on biotin for radiolabels in columns 1-3 in the section entitled "BACKGROUND OF THE INVENTION" and also gives a reasonable expectation of success for this substitution via numerous examples therein.

Thus, it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the compositions composed of bridging and signalling entities using non-radioactive labels for detection as instantly claimed because Dunn et al.(1977) disclose bridging and signalling entities as instantly claimed with radiolabel mediated detection and Ward et al. disclose both the motivation and reasonable expectation of success for substituting non-radioactive labels such as biotin for radiolabel mediated detection during hybridization procedures resulting therefore in the practice of the instantly claimed invention. It is noted that the labelled signal entities of Dunn et al. are disclosed as a nick translated preparation of molecules but that this is not outside of the

scope of the instantly rejected claims as noted above. The nick translated signalling entities are a heterogeneous mixture of various different fragments produced by the nick translation processing. These fragments hybridize to different segments of the bridging entity within the target sequence thereon due to their heterogeneous fragment nature but yet directed to said target. Since the nick translation process is variable regarding the number of nucleic acid fragments made thereby the process reasonably results in many different ratios regarding hybridized segments in the bridging entity as well as how many signalling entities there are relative to the bridging entities thus suggesting a wide range of ratios as given in a number of the instant claims between different parts of the instant invention. Instant claims such as claim 334 are included as rejected hereinunder due to the above noted unclarity regarding the word "derived".

This application is a continuation under 37 CFR § 1.60. Therefore references made of record in prior parent applications are hereby also made of record as having been considered in the instant application. However, since this application has been filed under 37 CFR § 1.60 none of the PTO Form 1449s or 892s from prior parent applications are in the instant file. Applicants are therefore requested to supply copies of the executed 1449s and 892s from these parent applications so that they may be included for reference to citations in the instant file.

No claim is allowed.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 305-7401 or (703) 305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703) 308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Chemical Matrix receptionist whose telephone number is (703) 308-0196.

March 10, 1997

Ardin H. Marschel

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